Original Study

A Pilot Trial of Cisplatin/Etoposide/Radiotherapy Followed by Consolidation Docetaxel and the Combination of Bevacizumab (NSC-704865) in Patients With Inoperable Locally Advanced Stage III Non–Small-Cell Lung Cancer: SWOG S0533

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Abstract

The incorporation of bevacizumab with concurrent chemoradiotherapy (CRT) in the treatment of locally advanced non–small-cell lung cancer (NSCLC) could improve efficacy in this disease stage. In this trial we accrued patients in 2 strata (high and low risk for hemoptysis) and in 3 separate cohorts depending on the timing of the bevacizumab. Bevacizumab could not be safely integrated or effectively combined with CRT in inoperable NSCLC patients. Future trials combining bevacizumab and CRT are not warranted.

Background: The aim of this trial was to determine feasibility of incorporating bevacizumab (B) into concurrent chemoradiotherapy (CRT) for locally advanced non–small-cell lung cancer (NSCLC). **Patients and Methods:** Patients with unresectable stage III NSCLC, performance status of 0 to 1, and adequate organ function were accrued in 2 strata, low- and high-risk (squamous histology, hemoptysis, tumor with cavitation and/or adjacent to a major vessel). Cohort 1 patients received cisplatin 50 mg/m^2 days (d) 1 and 8, etoposide 50 mg/m^2 (d 1-5) for 2 cycles concurrent with radiotherapy (64.8 Gy) followed by docetaxel (D) 75 mg/m^2 and B 15 mg/kg for 3 cycles. If safety was established, then accrual would continue to cohort 2 (B, d 15, 36, 57) and then subsequently to cohort 3 (B, d 1, 22, 43). **Results:** Twenty-nine patients (17 low- and 12 high-risk) registered to cohort 1. Twenty-six patients (including 4 squamous, 1 adenosquamous) were assessable. Twenty-five completed CRT. Grade 3/4 toxicities during CRT included acceptable rates of hematologic toxicity, esophagitis, and pneumonitis. Of 21 assessable for safety with D/B consolidation, major adverse events were pneumonitis (2 Grade 3) and 2 episodes of fatal hemoptysis in the high-risk group, resulting in closure of this stratum. The low-risk stratum subsequently closed because of slow accrual. Median overall survival was 46 months for low-risk and 17 months for high-risk strata. **Conclusion:** Bevacizumab was not safely integrated into CRT for stage III NSCLC in patients considered at high risk for hemoptysis. In lower risk patients, data are insufficient to determine safety or efficacy.

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Introduction

The standard treatment for patients with good performance status with inoperable stage III non–small-cell lung cancer (NSCLC) is concurrent chemoradiotherapy (CRT).[1,2] Despite the advances made with concurrent therapy, a great proportion of patients continue to die from recurrent disease, indicating that new treatment strategies are necessary. Optimal chemotherapeutic regimens and radiotherapy dose and schedules remain to be defined. Ongoing trials are incorporating newer chemotherapeutic and molecularly targeted agents into combined modality therapy with thoracic radiotherapy in an attempt to improve therapeutic outcomes.

The underlying hypothesis for Southwestern Oncology Group (SWOG)-coordinated studies of CRT in unresectable stage III NSCLC include full-dose chemotherapy given during concurrent thoracic radiation to optimize efficacy by addressing locoregional disease and distant micrometastases early on. Based on these concepts, the SWOG has pursued a strategy of combining cisplatin and etoposide with radiation in a series of sequential studies: S9019, S9504, and S0023.[3-6] Both drugs can be safely delivered with concurrent thoracic radiation at systemic doses. Pertinent to this study design was S9504, in which patients were treated with concurrent therapy followed by consolidation docetaxel.[4] Docetaxel was selected for this consolidation approach based on its clinical activity in second-line therapy (after failure of platinum-based treatment).[7,8] The long-term results of this phase II study demonstrated tolerability and efficacy with a median survival of 26 months and an overall survival (OS) of 29% at 5 years.[5] In a follow-up intergroup study, S0023, patients were treated with the S9504 regimen and then randomized to receive gefitinib or placebo as maintenance therapy.[6] Although this study did not demonstrate efficacy of gefitinib, results confirmed favorable outcomes with the S9504 approach. A subsequent Hoosier Oncology Group (HOG) phase III trial evaluating consolidation docetaxel was ongoing at the time S0533 was designed. Hence, the S9504 platform was used as the basis for the S0533 trial described herein.

Many research efforts have been focused on developing treatments based on the inhibition of tumor angiogenesis. Vascular endothelial growth factor (VEGF) is an ideal target because it is the most potent and specific of the endothelial mitogens.[9] Its presence has been correlated with a poor prognosis, and many human tumors, including NSCLC, have upregulated VEGF mRNA.[10,11] Bevacizumab is a humanized monoclonal antibody directed against VEGF.[12] In a randomized phase II trial, bevacizumab was combined with carboplatin and paclitaxel in chemotherapy-naive patients with advanced NSCLC.[13] The study suggested that bevacizumab at 15 mg/kg given every 3 weeks with chemotherapy might increase response and prolong time to progression. However, an increased incidence of pulmonary hemorrhage occurred that was associated with centrally located masses and/or cavitary lesions and 4 of 6 of these patients had squamous cell carcinoma histology. The risk of pulmonary hemorrhage in the squamous subset was 31% compared with 4% for the other pathologic subtypes. As a result, in the subsequent phase III trial, Eastern Cooperative Oncology Group E4599, patients who had lung cancer of squamous histology were excluded.[14] Results of this study indicated that patients who received carboplatin/paclitaxel with bevacizumab had a significantly better survival compared with those who received chemotherapy alone, resulting in subsequent approval of this regimen by the US Food and Drug Administration for the treatment of metastatic, nonsquamous NSCLC.

In addition to synergy with chemotherapeutic agents, there are data in preclinical models that suggest that inhibition of angiogenesis might potentiate radiation.[15,16] Vascular endothelial growth factor receptor inhibitors have been evaluated in preclinical lung cancer models and have shown tumor growth delay when given with radiation, especially on a concurrent treatment schedule.[17] Building on emerging data with bevacizumab in the metastatic setting, it would seem logical to try to incorporate bevacizumab into treatment for locally advanced NSCLC in an effort to increase the therapeutic ratio. This pilot study was designed to define the appropriate timing for the addition of bevacizumab onto our standard platform of full-dose concurrent CRT, and to delineate the tolerability of this approach in patients with NSCLC of all histologies. It was postulated that by radiating the primary tumor there would be a reduced occurrence of the pulmonary hemorrhage associated with bevacizumab treatment. The safe, successful incorporation of bevacizumab into this treatment paradigm could ultimately result in more efficacious management of unresectable NSCLC.

Patients and Methods

Patient Eligibility

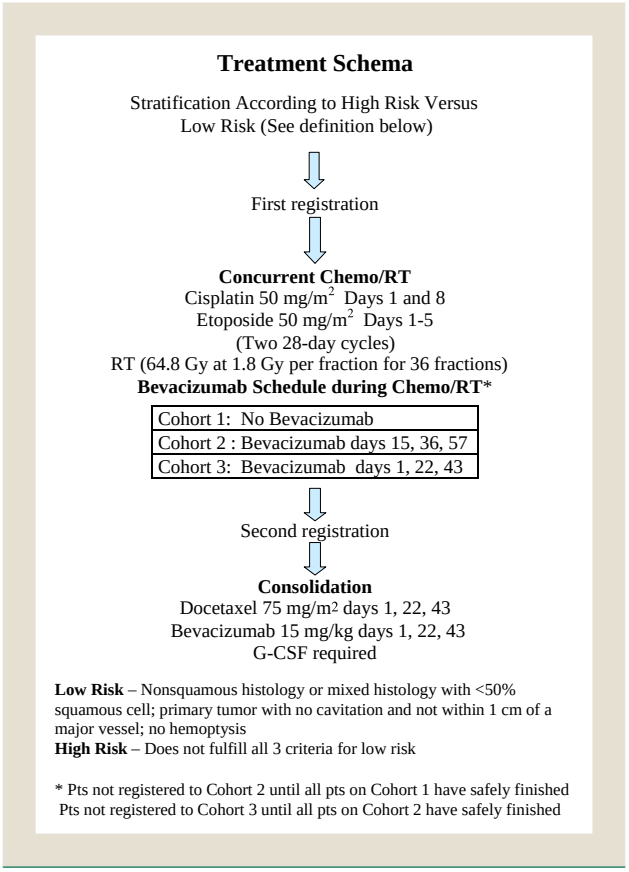
Patients with histologic or cytologic proof of unresectable stage IIIA (N2) or stage IIIB NSCLC with measurable or nonmeasurable disease were eligible. Lymph nodes were considered positive if histologically proven, $>$ 1 cm and positron emission tomography-positive, and/or $>$ 3 cm on computed tomography (CT) scan. Mediastinoscopy was not required for confirmation of N2 status. Additional eligibility criteria included a Zubrod performance status of 0 to 1; no previous chemotherapy, radiotherapy, or surgical resection for lung cancer; and adequate organ function. Patients had to have a forced expiratory volume in 1 second (FEV1) $\geq$ 2 L or a predicted FEV1 in the contralateral lung of $\geq$ 0.8 L. No full-dose anticoagulation or pathologic condition that carried a high bleeding risk, ulcer, nonhealing wound, or bone fracture was allowed. Patients could not have had a fine needle/core biopsy, or mediastinoscopy within 7 days of registration.

The protocol was approved by institutional review boards at each site, and was registered with ClinicalTrials.gov (ClinicalTrials.gov Identifier: NCT00334815) before enrollment of patients. All patients were informed of the investigational nature of the trial and provided written informed consent. Patients were offered optional participation in SWOG S9925 (Lung Cancer Specimen Repository).

Study Treatment

The treatment plan is depicted in Figure 1. All patients received concurrent chemotherapy and radiotherapy. Chemotherapy consisted of cisplatin 50 mg/m^2 on days 1, 8, 29, and 36 with etoposide 50 mg/m^2 on days 1 to 5 and 29 to 33. Thoracic radiotherapy commenced within 24 hours of chemotherapy. Radiation field arrangements were determined using 3-D planning to the primary lesion and involved lymph nodes. The radiation prescription was

Figure 1 Treatment Schema of SWOG 0533



Abbreviations: Chemo = Chemotherapy; G-CSF = Granulocyte Colony-Stimulating Factor; pts = Patients; RT = Radiation Therapy.

64.8Gy, given in 36 fractions at 1.8Gy/d, 5 days a week without interruption.

Four to 7 weeks after completion of radiation, patients without progressive disease according to Response Evaluation Criteria in Solid Tumors (RECIST) were registered to receive 3 cycles of docetaxel 75 mg/m^2 on day 1 of every 21 days. Prophylactic use of granulocyte colony-stimulating factor (G-CSF) was required with all 3 cycles of docetaxel consolidation.

Patient accrual proceeded in 3 sequential cohorts stratified according to high-risk versus low-risk patients. Patients were classified as low-risk if all of the following criteria were met: (1) nonsquamous histology or mixed histology with $<$ 50% squamous cell carcinoma; (2) a primary tumor with no cavitation and not within 1 cm of a major blood vessel; and (3) no history of hemoptysis (bright red blood of half a teaspoon or more) within 28 days before registration. Patients who did not fulfill all 3 of the low-risk category criteria were classified as high-risk. The treatment plan for the 3 cohorts differed only with regard to the timing of the bevacizumab. The first patient cohort would receive bevacizumab 15 mg/kg only during consolidation docetaxel after completion of concurrent CRT. If safe, based on predefined protocol-specific criteria, the second cohort would receive bevacizumab starting on day 15 of induction CRT. The last cohort of patients would start bevacizumab on day 1 of CRT. Accrual to any subsequent cohort of either stratum did not occur until safety data from the previous cohorts in both strata and other trials had been reviewed. The intent of this approach was to provide a more controlled setting for the addition of bevacizumab to combined modality treatment of all NSCLC histologies.

Toxicity Evaluation and Treatment Modifications

This study used the National Cancer Institute Common Toxicity Criteria version 3.0 for toxicity and adverse event reporting. During concurrent CRT, cisplatin was omitted on day 8 or 36 for Grade 4 or febrile neutropenia, Grade 4 esophagitis, or Grade $\geq$ 2 renal toxicity. On day 29, chemotherapy was delayed 1 week for an absolute neutrophil count $<$ 1500/μL, a platelet count $<$ 100,000/μL, or Grade $\geq$ 3 nonhematologic toxicity. If febrile neutropenia occurred during the previous cycle, etoposide was reduced to 4 days. Cisplatin dose was reduced or omitted if the creatinine clearance was $\leq$ 45 cc/min. A break in radiation was allowed only for Grade 4 neutropenia or esophagitis requiring parenteral alimentation.

Patients could not have persistent or new hemoptysis or Grade $>$ 2 esophagitis before going on to docetaxel consolidation. Patients who developed febrile neutropenia, or Grade 4 neutropenia or thrombocytopenia during consolidation required a dose reduction to 55 mg/m^2.

When the patient received the first dose of bevacizumab, toxicities were assessed weekly. These toxicities were reported using a Web-based dose-limiting toxicity reporting form. Before each treatment, there was special attention given to blood pressure, proteinuria, bleeding, cardiovascular events, reversible posterior leukoencephalopathy syndrome, esophagitis, esophageal stricture, and tracheoesophageal (TE)/bronchial fistulae.

Study Evaluation and Follow-Up

Prestudy evaluation included a medical history and physical examination, performance status determination, laboratory analysis, pulmonary function tests, electrocardiogram, a magnetic resonance imaging or CT scan of the brain, and a CT scan of the chest including the liver and adrenal glands. During CRT, complete blood counts were obtained weekly and, during consolidation, before each cycle and during week 2. A history and physical, and chemistries were obtained before each treatment cycle. When bevacizumab was started, weekly toxicity assessments were required and continued until 60 days after the bevacizumab was discontinued or until all adverse events had resolved. Response assessment occurred at the end of CRT and docetaxel/bevacizumab treatment and then every 2 to 3 months for 2 years, and then every 6 months until 4 years after the initial registration.

Statistical Methods

The primary objective was to assess toxicities, especially the risk of hemorrhage, associated with the combination of bevacizumab with combined modality therapy. This would be assessed in up to 3 different cohorts to determine the earliest time point tolerable to incorporate bevacizumab. Initially, 35 low-risk and 35 high-risk patients would be accrued to the first cohort assuming that 80% would be registered for consolidation therapy and be evaluable for bevacizumab-associated toxicities. If the first cohort was deemed safe, then an additional 28 evaluable patients per stratum would be

accrued to the second cohort. If the second cohort was determined to be tolerable, then another 28 patients per stratum would be accrued to the third cohort. The design was sufficient to distinguish between the null hypothesis of an unacceptable rate ($\geq$ 20%) of Grade $\geq$ 4 hemorrhage versus the alternative hypothesis of an acceptable rate ($\leq$ 5%) of these toxicities with 84% exact power, using a 1-sided test based on binomial distribution with a significance of 5%. Progression-free survival (PFS) and OS were measured from the date of initial enrollment. Estimates were calculated using the method of Kaplan–Meier.[18] Confidence intervals (CIs) for the median PFS and OS estimates were constructed using the method of Brookmeyer–Crowley.[19] The response rate (RR) was defined as the number of confirmed and unconfirmed complete and partial responses (PRs) among the subset of patients with measurable disease (according to RECIST) at baseline. The disease control rate (DCR) was defined as the number of patients with a best response of stable disease or better among the patients with measurable disease at baseline. Clopper–Pearson (exact) 95% CIs were calculated for binary outcomes, such as RR, DCR, and individual toxicity rates.

Table 1 Patient Characteristics

	Low Risk (n = 15)	High Risk (n = 11)
Mean Age, Years (Range)	54.5 (32-70)	63 (51-77)
Male Sex, n (%)	6 (40)	7 (64)
White Race, n (%)	14 (93)	9 (82)
PS = 0, n (%)	9 (60)	5 (45)
Histology		
Adenocarcinoma	10	3
Squamous	0	4
Large Cell	1	1
Mixed	1	0
Other	3	3
Stage		
IIIA	6	1
IIIB	9	9
Unknown	–	1

Abbreviation: PS = performance status.

Results

Trial History

Southwestern Oncology Group trial 0533 was activated in June 2006. Because of concerns regarding toxicity monitoring, the trial was initially opened at a limited number of SWOG institutions. The study was temporarily closed April 2007 secondary to a Cancer Therapy Evaluation Program action letter regarding reports of TE fistulae in patients with small-cell lung cancer (SCLC) treated with concurrent CRT and bevacizumab. Additionally, there were multiple amendments throughout the study course because of new reports of bevacizumab-related toxicity. When it was deemed that the trial could be conducted safely and toxicities could rapidly be communicated, it was opened group-wide in June 2008. The high-risk stratum closed secondary to toxicity in March 2009 and the low-risk stratum closed in March 2010 because of slow accrual. Patients were enrolled only to cohort 1.

Patient Characteristics

Sixteen patients were accrued to the low-risk stratum and 15 were eligible. In the high-risk stratum there were 13 patients, 12 eligible. Of the 3 ineligible patients, 2 had incorrect stage and 1 had inadequate pulmonary function. One high-risk patient never received any treatment. The characteristics of the 26 assessable patients are presented in Table 1. In the high-risk stratum, there was a greater proportion of men and patients with stage IIIB cancer. There were 4 patients with squamous cell carcinoma in this stratum.

Twenty-six patients completed the CRT as planned. There was 1 major protocol deviation: a patient in the initial cohort received 1 dose of bevacizumab concurrent with CRT due to a treatment assignment error.

Fourteen patients from the low-risk stratum and 7 high-risk patients were treated with consolidation docetaxel and bevacizumab. Nine and 3 patients, respectively, completed the consolidation treatment as planned. Reasons for incompletion of treatment included 5 for adverse events, 2 deaths, 1 patient refusal, and 1 patient who developed a cavitating lesion.

Toxicity

Grades 3 and 4 toxicities that occurred during concurrent CRT and the consolidation phase of treatment are presented in Table 2. Overall, the concurrent CRT was well tolerated. Grades 3 or 4 neutropenia or leukopenia were the most common toxicities and occurred in 6 (38%) and 4 (23%) of the patients, respectively. There was an 3 (11.5%) incidence of Grade 3 to 4 febrile neutropenia. Grade 3 esophagitis occurred in only 2 patients (8%) and there was 1 episode of Grade 3 pneumonitis.

During the consolidation docetaxel and bevacizumab treatment there was no significant neutropenia or leukopenia, likely as a result of the mandated use of pegfilgrastim or G-CSF. There were 2 episodes of Grades 3 and 4 anemia. No further esophagitis occurred during the consolidation treatment. There were an additional 2 instances of Grade 3 pneumonitis for a total incidence of 11.5% over both treatment phases.

There were 2 episodes of Grade 5 pulmonary hemorrhage. Both occurred in high-risk patients and resulted in the closure of this stratum. One patient had squamous cell carcinoma with cavitation, with the event occurring 13 days after the second cycle of consolidation treatment. The second patient had adenocarcinoma and a centrally located tumor. Fatal hemoptysis developed 29 days after the second consolidation cycle. The third cycle of consolidation had already been delayed because of a hospitalization for pneumonia. During consolidation therapy there was 1 episode of Grade 3 gastrointestinal hemorrhage in a high-risk patient. There were an additional 3 occurrences of Grade 1 upper/lower respiratory tract bleeding among the low-risk patients. There was only 1 incidence of Grade 1 proteinuria and no vascular events.

Efficacy

Twenty-four patients had measurable disease at baseline and were included in the analysis of response. Nine of 14 patients on the low-risk stratum had either a confirmed or unconfirmed PR for a RR of 64% (95% CI, 35%-87%). Seven of 10 high-risk patients had a PR

Table 2 Toxicities

Treatment	Chemo/RT						Consolidation					
Stratum	Low Risk (n = 15)			High Risk (n = 11)			Low Risk (n = 14)			High Risk (n = 7)		
Toxicity Grade	3	4	5	3	4	5	3	4	5	3	4	5
Toxicity												
Neutropenia	3	1	–	3	3	–	–	–	–	–	–	–
Leukopenia	1	2	–	2	1	–	–	–	–	–	–	–
Thrombocytopenia	2	–	–	–	–	–	–	–	–	–	–	–
Anemia	1	–	–	1	–	–	–	–	–	1	1	–
Febrile Neutropenia	–	–	–	2	1	–	–	–	–	–	–	–
Electrolytes	2	–	–	2	–	–	–	–	–	1	–	–
Renal	–	–	–	1	–	–	–	–	–	–	–	–
Nausea	1	–	–	1	–	–	–	–	–	–	–	–
Esophagitis	1	–	–	1	–	–	–	–	–	–	–	–
Pneumonitis	–	–	–	1	–	–	1	–	–	1	–	–
Hemorrhage	–	–	–	–	–	–	–	–	–	**1**	–	**2**[a]

Abbreviations: Chemo = chemotherapy; RT = radiation therapy.
[a](1) Adenocarcinoma, central tumor, Grade 5 hemoptysis 29 days after cycle 2; (2) squamous cancer, cavitation, Grade 5 hemoptysis 13 days after cycle 2.

for a RR of 70% (95% CI, 35%-93%). The DCRs were 93% (95% CI, 66%-100%) and 90% (95% CI, 56%-100%), respectively.

The median PFS was 38 months (95% CI, 23-46 months) for the low-risk patients and 15 months (95% CI, 5-17-months) for the high-risk patients (Figure 2). Median OS was 46 months (95% CI, 26-51 months) for the low-risk stratum and 17 months (95% CI, 5-18 months) for the high-risk stratum (Figure 3).

Discussion

The SWOG has had success with incorporating full-dose cisplatin and etoposide chemotherapy with radiation as treatment for locally advanced NSCLC with acceptable rates of hematologic toxicity, esophagitis, and pneumonitis. A randomized phase III HOG study designed to validate the concept of docetaxel consolidation, ongoing at the time S0533 was activated, did not support the use of docetaxel consolidation treatment because there was no significant difference in survival between the treatment arm that received the docetaxel compared with the study arm that did not receive additional chemotherapy after CRT.[20] It is important to note that despite the results of the HOG study, consolidation therapy after concurrent CRT is consistently used in trial designs for the treatment of locally advanced NSCLC. Interestingly, patients in

Figure 2 Progression-Free Survival for the Low- and High-Risk Strata

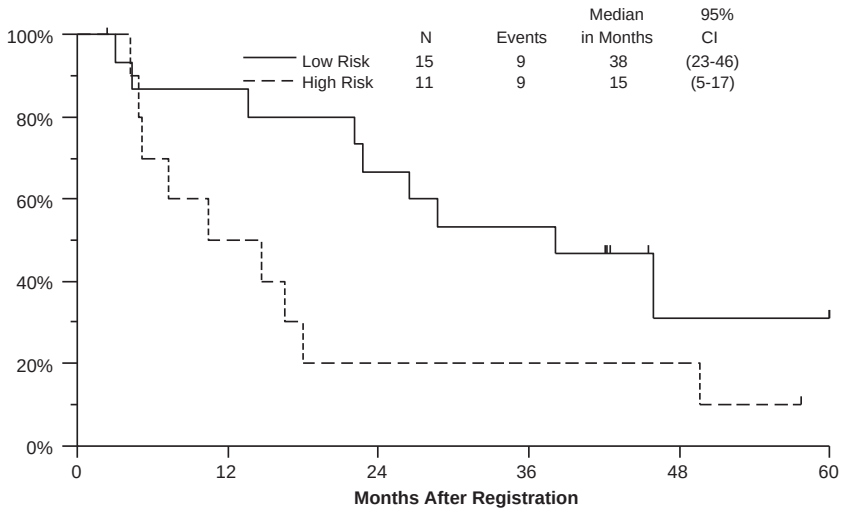
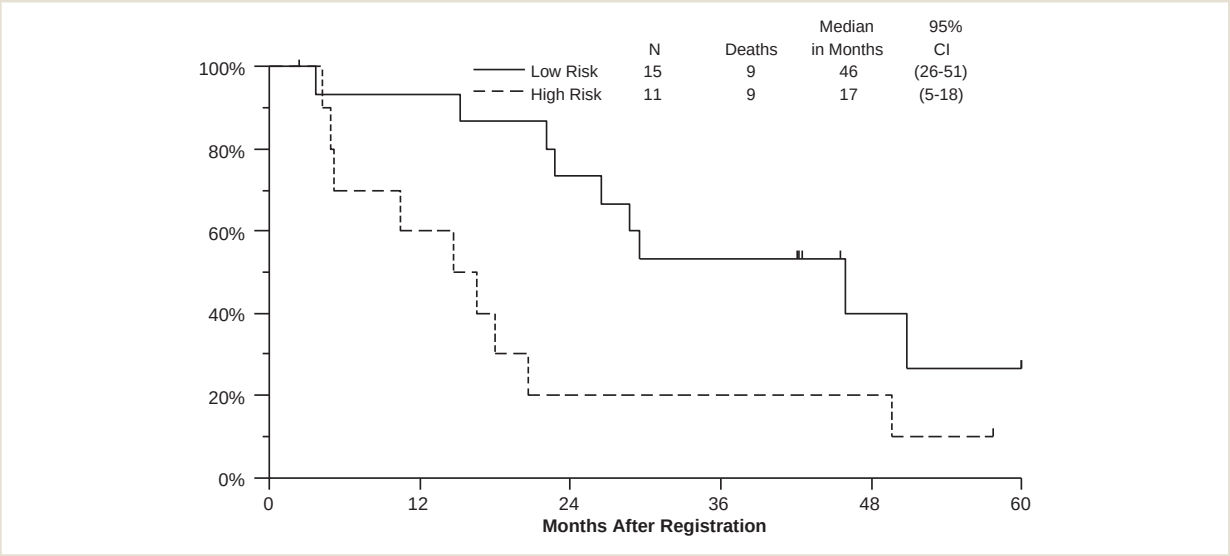


Figure 3 Overall Survival for the Low- and High-Risk Strata



the HOG trial who did not receive consolidation docetaxel still had a 23.2-month median survival which further supports the CRT cisplatin-etoposide platform used in these trials.

Some of the most recent advances in the treatment of NSCLC have centered on the development of a number of molecularly-targeted agents such as inhibitors of VEGF and epidermal growth factor receptor. Thus, it was rational to attempt to include these novel drugs in the treatment of locally advanced disease in an attempt to improve cure rates. Bevacizumab carries with it some unique and disturbing toxicities, particularly pulmonary hemorrhage, which prevents its use in many patients with NSCLC.[13,21] There was very little information regarding the use of bevacizumab in conjunction with radiation and chemotherapy in the treatment of locally advanced disease at the time this protocol was initiated. We elected to take a cautious approach by initially administering bevacizumab with consolidation chemotherapy after the conclusion of the concurrent CRT. Our rationale was based on the evidence that palliative radiotherapy is effective in controlling hemoptysis. A meta-analysis of 9 trials showed symptom improvement in 80% of patients and 5 trials reported complete resolution of bleeding in 74% of patients who received low-dose radiation (10-30 Gy) and 69% of patients who received higher-dose radiation.[22] Death from pulmonary hemorrhage after definitive CRT is rare, albeit data on this subject are lacking. In the HOG trial and S0023 in which all patients received CRT, no toxic deaths were reported from pulmonary hemorrhage.[6,20] A single-institution retrospective analysis from Korea attempted to identify risk factors for fatal hemoptysis associated with CRT.[23] There was an 8% incidence of fatal pulmonary hemorrhage. A multivariate analysis identified central tumor location and poor performance status as risk factors for fatal hemoptysis. Although histology was not a significant variable, 10 of the 12 affected patients had squamous cell histology and most of the patients had radiographic evidence of radiation pneumonitis/fibrosis. The successful conduct of a trial with significant safety concerns in a cooperative group setting is a daunting task. To ensure careful monitoring of all toxicities especially during bevacizumab treatment, a Rapid Toxicity Reporting Form had to be submitted weekly on all patients when bevacizumab treatment commenced. A summary report of all significant toxicities was generated and sent to the study coordinators on a weekly basis. The trial was also initially opened in a limited number of institutions to ensure that the reporting system that was developed was feasible and would result in the timely collection of toxicity data. Despite this cautious stepwise design, 2 episodes of fatal hemoptysis occurred among the high-risk patients in the first study cohort, resulting in immediate closure of this stratum. Both events occurred at the same time during consolidation after 2 cycles of chemotherapy and bevacizumab. Treating the primary tumor with CRT did not prevent the subsequent occurrence of fatal pulmonary hemorrhage.

Other investigators have also been unable to integrate bevacizumab into a CRT regimen for locally advanced disease in a fashion enabling transition to clinical practice. Socinski et al recently reported the results of a 45-patient trial in locally advanced NSCLC.[24] Patients in this study received induction carboplatin/paclitaxel/bevacizumab followed by weekly carboplatin/paclitaxel and bevacizumab (every other week) with or without erlotinib with 74 Gy thoracic conformal radiation and then consolidation bevacizumab and erlotinib. The study was closed for patients with squamous cell histology after 2 Grade 5 hemorrhagic events, both of which occurred after CRT, 78 and 69 days after the last dose of bevacizumab. There was also an additional episode during concurrent treatment.

Another toxicity of concern during the course of the trial was the development of TE fistulae, which is generally an uncommon event as a result of CRT for lung cancer treatment. In a simultaneous, ongoing study in limited stage SCLC, among 29 patients there were 2 confirmed and 1 suspected episode of TE fistulae.[25,26] All 3 patients had Grade 3 esophagitis during CRT and bevacizumab

induction therapy. Subsequently, an additional patient developed a fatal TE fistula during maintenance treatment. There was some speculation that this toxicity might be histology related. However, in an independent study in NSCLC, 2 of 5 patients developed TE fistulae during maintenance treatment with chemotherapy and bevacizumab.[26] Both patients also had severe esophageal toxicity after CRT and bevacizumab. The insinuation is that severe esophageal toxicity as a result of this treatment might predispose patients to the development of TE fistulas. In the trial by Socinski et al, the Grade 3/4 esophagitis rate was 29% and there was 1 TE fistula 3.5 months after CRT.[24] No patients in our study developed TE fistulae, most likely because the trial was amended to exclude patients with Grade $>$ 2 esophagitis from receiving bevacizumab.

It is difficult to ascertain if the addition of bevacizumab was efficacious in the treatment of the patients in the low-risk stratum. The median progression-free and OS estimates for the low-risk patients were 38 and 46 months, which are much better than in previous trials, but might be a product of the small number of patients accrued. This study still supports the use of cisplatin/etoposide and concurrent radiotherapy as an effective treatment. The nonsquamous group in the previously referenced trial from Socinski et al had an 18.7-month median OS and a 21% 5-year survival,[24] which was no better than results from previous trials.[27]

There are several important lessons learned from the conduct of S0533. First, we were unable to successfully integrate bevacizumab into concurrent CRT for stage III NSCLC, particularly in patients considered at high risk for pulmonary hemorrhage (ie, squamous cell carcinoma histology, central tumors, tumor cavitation). For patients considered lower-risk, the data are insufficient to determine efficacy or safety.

Caution should be taken when using bevacizumab for recurrent disease after previous treatment with concurrent CRT, assuming the primary endobronchial tumor remains. This might be especially true in patients who experienced severe esophagitis and/or pneumonitis during or after concurrent therapy considering several of the reported events of pulmonary hemorrhage and TE fistulae occurred long after initial treatment was complete.

Conclusion

There are numerous new molecularly targeted agents that are of interest in the treatment of NSCLC. With many of them, especially those with antiangiogenic activity, careful study design and close toxicity monitoring is imperative to properly integrate their use in multimodality therapy. Our experience with SWOG S0533 indicates that, with very careful planning, a trial of this nature can be safely conducted within a cooperative group setting.

Clinical Practice Points

- Concurrent CRT is the standard of care treatment for patients with good performance status with locally advanced, inoperable NSCLC. Bevacizumab combined with chemotherapy has resulted in an improvement in survival for patients with metastatic NSCLC.
- Our trial was conducted within the SWOG. Patients were identified as high- and low-risk for hemoptysis and were accrued separately to these strata. The study was designed to define the appropriate timing and safety of the combination of bevacizumab with the CRT platform.
- Bevacizumab could not be safely integrated with CRT for patients at high risk for hemoptysis. Among low-risk patients, the data were insufficient to determine efficacy. Other investigators have come to the same conclusion, that the incorporation of bevacizumab is not recommended in the treatment paradigm for locally advanced NSCLC.
- Trials that incorporate new agents that require close monitoring can be conducted within a cooperative group setting with the proper study design.

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Disclosure

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References

1. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non–small-cell lung cancer. *J Clin Oncol* 1999; 17:2692-9.
2. Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non–small-cell lung cancer: randomized phase III RTOG 9410. *J Natl Cancer Inst* 2011; 103:1452-60.
3. Albain KS, Crowley JJ, Turrisi AT, et al. Concurrent cisplatin, etoposide plus radiotherapy for pathologic stage IIIB non–small-cell lung cancer: a Southwest Oncology Group phase II study (S9019). *J Clin Oncol* 2002; 20:3454-60.
4. Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non–small-cell lung cancer: phase II Southwest Oncology Group study S9504. *J Clin Oncol* 2003; 21:2004-10.
5. Gandara DR, Chansky K, Albain KS, et al. Long-term survival with concurrent chemoradiation therapy followed by consolidation docetaxel in stage IIIB non–small-cell lung cancer: a phase II Southwest Oncology Group study (S9504). *Clin Lung Cancer* 2006; 8:116-21.
6. Kelly K, Chansky K, Gaspar LE, et al. Phase III trial of maintenance gefitinib or placebo after concurrent chemoradiotherapy and docetaxel consolidation in inoperable stage III non–small-cell lung cancer: SWOG S0023. *J Clin Oncol* 2008; 26:2450-6.
7. Gandara DR, Vokes E, Green M, et al. Activity of docetaxel in platinum-treated non–small-cell lung cancer: Results of a phase II multicenter trial. *J Clin Oncol* 2000; 18:131-5.
8. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non–small-cell lung cancer previously treated with platinum-based chemotherapy. *J Clin Oncol* 2000; 18:2095-103.
9. Folkman J, Shing Y. Angiogenesis. *J Biol Chem* 1992; 267:10931-4.
10. Toi M, Matsumoto T, Bando H. Vascular endothelial growth factor: its prognostic, predictive, and therapeutic implications. *Lancet Oncol* 2001; 2:667-73.
11. Yuan A, Yu CJ, Kuo SH, et al. Vascular endothelial growth factor 189 mRNA isoform expression specifically correlates with tumor angiogenesis, patient survival, and postoperative relapse in non–small-cell lung cancer. *J Clin Oncol* 2001; 19: 432-41.
12. Cababe E, Wakelee H. Role of anti-angiogenesis agents in treating NSCLC: focus on bevacizumab and VEGFR tyrosine kinase inhibitors. *Curr Treat Options Oncol* 2007; 8:15-27.
13. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non–small-cell lung cancer. *J Clin Oncol* 2004; 22:2184-9.
14. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non–small-cell lung cancer. *N Engl J Med* 2006; 355:2542-50.

15. Geng L, Donnelly E, McMahon G, et al. Inhibition of vascular endothelial growth factor receptor signaling leads to reversal of tumor resistance to radiotherapy. *Cancer Res* 2001; 61:2413-9.
16. Gorski DH, Beckett MA, Jaskowiak NT, et al. Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. *Cancer Res* 1999; 59:3374-8.
17. Williams KJ, Telfer BA, Brave S, et al. ZD6474, a potent inhibitor of vascular endothelial growth factor signaling, combined with radiotherapy: schedule-dependent enhancement of antitumor activity. *Clin Cancer Res* 2004; 10: 8587-93.
18. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53:457-81.
19. Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics* 1982; 38:29-41.
20. Hanna N, Neubauer M, Yiannoutsos C, et al. Phase III study of cisplatin, etoposide, and concurrent radiation with or without consolidation docetaxel in patients with inoperable stage III non–small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol* 2008; 26:5755-60.
21. Sandler AB, Schiller JH, Gray R, et al. Retrospective evaluation of the clinical and radiographic risk factors associated with severe pulmonary hemorrhage in first-line advanced, unresectable non–small-cell lung cancer treated with carboplatin and paclitaxel plus bevacizumab. *J Clin Oncol* 2009; 27:1405-12.
22. Fairchild A, Harris K, Barnes E, et al. Palliative thoracic radiotherapy for lung cancer: a systemic review. *J Clin Oncol* 2008; 26:4001-11.
23. Kim YH, Kim EY, Ban HJ, et al. Risk factors for fatal hemoptysis after concurrent chemoradiation therapy in patients with non–small-cell lung carcinoma. *Chonnam Med J* 2010; 46:19-24.
24. Socinski MA, Stinchcombe TE, Moore DT, et al. Incorporating bevacizumab and erlotinib in the combined-modality treatment of stage III non–small-cell lung cancer: results of a phase I/II trial. *J Clin Oncol* 2012; 30:3953-9.
25. Patton JF, Spigel DR, Greco FA, et al. Irinotecan (I), carboplatin (C), and radiotherapy (RT) followed by maintenance bevacizumab (B) in the treatment (tx) of limited-stage small-cell lung cancer (LS-SCLC): update of a phase II trial of the Minnie Pearl Cancer Research Network (abstract 7085). *J Clin Oncol* 2006; 24:385a.
26. Spigel DR, Hainsworth JD, Yardley DA, et al. Tracheoesophageal fistula formation in patients with lung cancer treated with chemoradiation and bevacizumab. *J Clin Oncol* 2009; 28:43-8.
27. Socinski MA, Morris DE, Halle JS, et al. Induction and concurrent chemotherapy with high dose conformal radiation in unresectable stage IIIA and IIIB non–small-cell lung cancer: a dose escalation phase I/II trial. *J Clin Oncol* 2004; 22:4341-50.